EXHIBIT A

Skip over navigation

Cosolvents and Cosolvency

Author: Joseph T. Rubino[a]

Abstract

Cosolvents are defined as water-miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water-soluble substances or to enhance the chemical stability of a drug. Cosolvency, then, refers to the technique of using cosolvents for the stated purposes; it is also commonly referred to as solvent blending. Cosolvency has been used as an approach for preparing liquid drug preparations throughout the history of drug formulation. Certain drugs of botanic origin were known to be poorly soluble in water and required formulation in water-ethanol mixtures in order to deliver an adequate dose of drug in a small volume of preparation. A common example of a class of formulation containing cosolvents is the elixir, which by definition is a sweetened, hydroalcoholic solution intended for oral use. Tinctures, which generally contain even higher amounts of alcohol, are another classic example of a liquid dosage form containing a cosolvent. The need to employ cosolvents in the formulation of new drugs as solutions for oral, parenteral, and topical use remains high, especially with the increasing structural complexity of new therapeutic agents.

In many cases, cosolvency can increase the solubility of a non-polar drug up to several orders of magnitude above the aqueous solubility. This would be significant, for example, in a formulation problem where it might be necessary to increase the solubility of a drug 500-fold or more. The use of cosolvents to prepare solution formulations of non-polar drugs is a simple and potentially effective way to achieve high concentrations of drug.

The primary disadvantages of cosolvency include the potential for biological effects and the potential for drugs that have been solubilized using cosolvents to precipitate upon dilution with aqueous fluids. The biological effects of a cosolvent that may limit or eliminate its use in drug formulations include their general toxicity, target organ toxicity, tissue irritation, or tonicity with respect to biologic membranes. In addition, precipitation of drug upon dilution with aqueous media or during injection or application to mucous membranes must always be considered in deciding if a cosolvent can be used as a vehicle forpoorly water-soluble drugs. Other considerations include the viscosity, tonicity, and taste, as well as the effect of cosolvents on the solubility and stability of formulation components other than the drug.

When used as a method for increasing the chemical stability of a drug, cosolvents may be effective by one or two mechanisms. If a drug is susceptible to hydrolytic degradation, cosolvents may reduce the degradation of the drug by substituting for some or all of the water in the formulation. Alternatively, a cosolvent may enhance the stability of a drug by providing a less suitable environment for the transition state of the reactants, provided the transition state is more polar than the reactants themselves.1

View Full Text Section

 **Download PDF** (~270 KB)  **View Article Online (HTML)**

Bookmark with:

- **Del.icio.us**
- **BibSonomy**
- **Connotea**
- **More bookmarks**

Affiliation: [a] Wyeth-Ayerst Research, Pearl River, New York, U.S.A.

DOI: 10.1081/E-EPT-100000466
Published in: **Encyclopedia of Pharmaceutical Technology**
Published on: 02 October 2006

- **Sign In**